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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,418	11/04/1999	JOEL B. EPSTEIN	244/023	2559

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Patent Administrator
Katten Muchin Zavis Rosenman
525 West Monroe
Suite 1600
Chicago, IL 60661-3693

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,418	EPSTEIN, JOEL B.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-11,19-21,23,24,27-29 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-11,19-21,23,24,27-29 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed February 10, 2005 have been entered.

Claims 1-3, 5-6, 9-11, 19-21, 23-24, 27-29 and 39 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 recites the limitation "non-steroidal anti-inflammatory agent" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-6, 9-11, 19-21, 23-24, 27-29 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitt et al. (USPN 5,540,931), Lozada, and Sharpe et al. (USPN 5,637,616) in view of Batt et al. (USPN 5,578,609).

Hewitt et al. (USPN 5,540,931) teaches topical compositions for site-specific immune suppression comprising one or more immunosuppressants, e.g., azathioprinse, cyclophosphamide, didemnin B, deoxyspergualin. Methotrexate, thalidomide, or

combinations thereof, see claims 1-7. Hewitt et al. also teaches the employment of hydrocortisone in its formulation, see claims7-9. Hewitt finally teaches that some conditions may require topical immunosuppresion alone, see col. 9, lines 19-21 for example.

Lozada teaches a method of treating patients with chronic inflammatory mucocutaneous disease having oral ulcerations including lichen planus, pemphigus vulgaris and bullous pemphigoid comprising administering azathioprine (an immunosuppressive agent), and a steroidal antiinflammatory agent see page 257 first full paragraph, see also MATERIALS AND METHODS. Lozada teaches that Azathioprine is administered from 5 mg every other day to 100 mg/day, see pages 258 Drugs and Results. See also page 259, Col. 2, first full paragraph as well as page 258 Adverse effects.

Sharpe et al. (USPN 5,637,616) teaches a method for topical treatment of mucosal lesions and in particular bullous pemphigoid, lichen planus, and aphthous ulcers employing gel, ointment, cream, foam, lotion or a solution that is orally applied, swished and expectorated or swallowed, see in particular claims 5-13. Sharpe et al. (USPN 5,637,616) also teaches that topical corticosteroids are known to be employed in treating aphthous ulcers, see col. 4, lines 41-47. Sharpe et al. (USPN 5,637,616) also teaches that bullous pemphigoid is known to be treated with immunosuppressive agents in addition to steroids and pemphigus is known to be treated with corticosteroids, such as prednisone and prednisolone as well as immunosupressive agents such as azathioprine, cyclosphamide, methotrexate and cyclosporine, see col. 3, lines 23-30;

see also col. 2, 62-col. 3, line 4. Sharpe et al. also teaches the employment of anti-inflammatory agents in its composition, see in particular col. 10 lines 51-56. Finally, Sharpe et al. teaches that these oral lesions are accompanied by pain, see col 1, lines 39-43, see also col. 5, lines 32-36.

Hewitt, Lozada and Sharpe et al. (USPN 5,637,616) taken together, do not particularly teach the incorporation of NSAIDS in their methods. The primary references do not expressly teach the active agents being swished in the mouth.

Batt et al. teaches a method of treating graft versus host disease employing immunosuppressants such as azathioprine and steroids with combination of NSAID such as aspirin, ibuprofen and naproxen (See col. 7, lines 4-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a liquid formulation comprising azathioprine (an immunosuppressive agent), corticosteroids, and NSAID in the herein claimed method of treating autoimmune diseases of the mouth. It would have also been obvious to employ NSAIDS in their method.

One of ordinary skill in the art would have been motivated to employ a liquid formulation comprising azathioprine (an immunosuppressive agent), corticosteroids, and NSAID in the herein claimed method of treating autoimmune diseases of the mouth because these agents individually are known to be useful in treating autoimmune diseases of the mouth. Combining two or more agents which are known to be useful to in treating autoimmune disease of the mouth individually into a single composition useful for the very same purpose is prima facie obvious (See *In re Kerkhoven* 205

USPQ 1069). Furthermore, the oral lesions symptomatic of autoimmune diseases of the mouth are known to be painful. The skilled artisan would have been motivated to add NSAIDS to formulations known to be useful in treating autoimmune diseases of the mouth because pain is known to be associated with these oral lesions. Optimization of amounts is within the purview of the skilled artisan and is therefore obvious. In addition, swishing the active in the mouth would be considered an alternative method to deliver the active in contact with the oral lesion. One of ordinary skilled in the art is in possession of conventional method of delivering active to the disease site. Therefore, absent evidence to the contrary, swishing the active in order for the active agents got in contact with the disease site would be considered an obvious alternative to one of ordinary skill in the art.

Response to Arguments

Applicant's arguments filed February 10, 2005 averring Hewitt's teaching cyclosporine in site-specific immune suppression have been considered, but are not found persuasive. Hewitt et al. actually teaches other immunosuppressants other than cyclosporine useful for site-specific immune suppression. Taken together with the teachings of theother prior arts, one of ordinary skill in the art would have been motivated to employ the here claimed agents in a method of treating autoimmune disease of the mouth.

Applicant's arguments filed February 10, 2005 averring the alleged deficiency of each cited references individually have been considered, but are not found persuasive. In response to applicant's arguments against the references individually, one cannot

show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the cited prior arts teach the herein claimed agents are all known to be useful in treating autoimmune conditions of the mouth. For example, Sharpe et al. teaches azathioprine as effective in treating autoimmune mouth lesions; Lozada teaches the local topical treatment of immunosuppressants including azathioprine in method of treating mucosal lesions; furthermore, Batt teaches azathioprine as useful in treating graft-vs-host disease. Therefore, employing them concomitantly together in a method useful for the very same purpose would been seen as prima facie obvious, absent evidence to the contrary (See *In re Kerkhoven* 205 USPQ 1069).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Primary Examiner
Art Unit 1617